

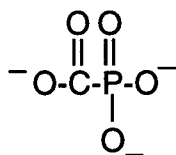
**METAL CATION MEDIATED HYDROLYSIS OF PHOSPHONO-
FORMATE DIESTERS: CHEMOSELECTIVITY AND CATALYSIS**

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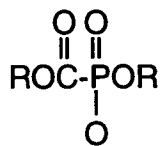
PHOSPHONOFORMATES



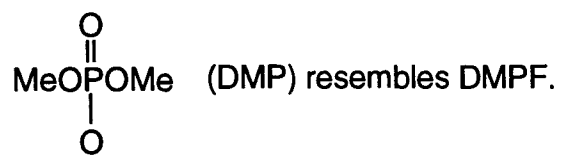
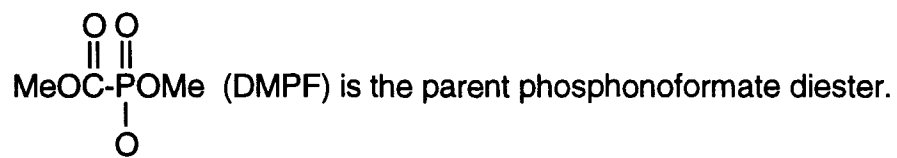
Phosphonoformate trianion ("Foscarnet") is an antiviral agent active against herpes simplex and AIDS-related cytomegalovirus.

Poor membrane permeability. Phosphonoformate diesters and triesters of interest as "prodrugs."

Monoanionic phosphonoformate *diesters* exhibit antiviral activity in prodrug studies.



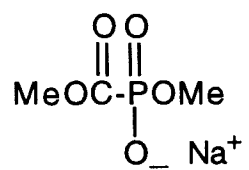
DIMETHYLPHOSPHONOFORMATE



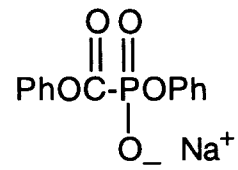
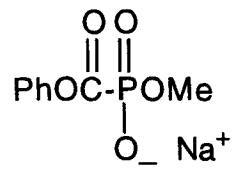
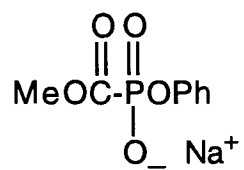
How will metal cation cleavage of DMPF compare to that of DMP?

DMPF has 3 sites for cleavage: O-C, P-O, and C-P. What sort of *chemoselectivity* can be observed?

SUBSTRATES AND METAL CATIONS



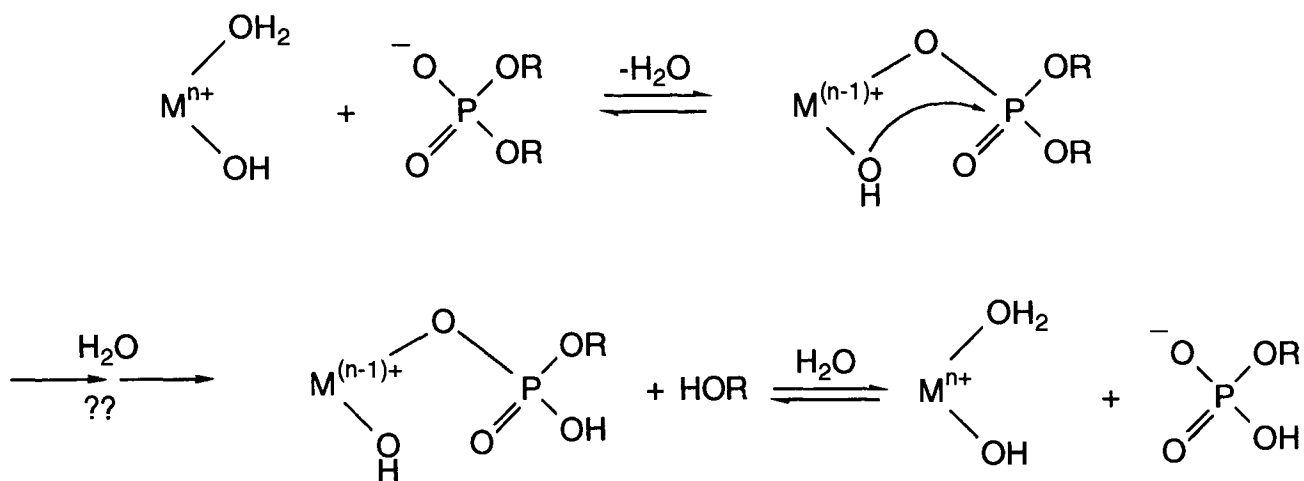
(DMPF)



Ce^{4+} Th^{4+} Zr^{4+} Hf^{4+}

Why these cations?

POLYVALENT METAL CATIONS CAN MEDIATE PHOSPHODIESTER HYDROLYSIS



M^{n+} provides electrophilic/nucleophilic catalysis. Require good Lewis acidity to bind $\text{P}-\text{O}^-$ and to acidify H_2O of hydration to afford metal bound OH nucleophile. Turnover catalysis is possible in some cases.

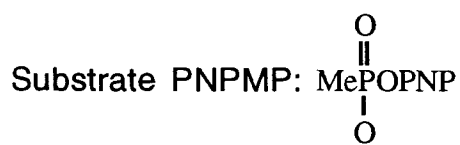
Desire highly charged, small M^{n+} ("hard" cation), but also with high-lying vacant d or f orbitals to bind $\text{P}-\text{O}^-$, *transition metals, lanthanides, or actinides*.

Most Commonly Employed Metal
Cations for Hydrolysis of Phosphodiester

1A 1 2A 2 3A 4A 5A 6A 7A 8A 9A 10A 11A 12A 13A 14A 15A 16A																	
1s 1, -1 1 H Hydrogen	2s 2 He Helium	3s 3 Li Lithium	3p 3 Be Beryllium	4s 4 Na Sodium	4p 4 Mg Magnesium	5s 5 K Potassium	5p 5 Ca Calcium	6s 6 Sc Scandium	6p 6 Ti Titanium	7s 7 V Vanadium	7p 7 Cr Chromium	8s 8 Mn Manganese	8p 8 Fe Iron	9s 9 Co Cobalt	9p 9 Ni Nickel	10s 10 Cu Copper	10p 10 Zn Zinc
11s 11 Al Aluminum	11p 11 Si Silicon	12s 12 Ga Gallium	12p 12 Ge Germanium	13s 13 As Arsenic	13p 13 Se Selenium	14s 14 Br Bromine	14p 14 Kr Krypton	15s 15 Rb Rubidium	15p 15 Sr Strontium	16s 16 Y Yttrium	16p 16 Zr Zirconium	17s 17 Nb Niobium	17p 17 Mo Molybdenum	18s 18 Tc Technetium	18p 18 Ru Ruthenium	19s 19 Rh Rhodium	19p 19 Pd Palladium
20s 20 Ag Silver	20p 20 Cd Cadmium	21s 21 In Indium	21p 21 Sn Tin	22s 22 Pb Lead	22p 22 Bi Bismuth	23s 23 Po Polonium	23p 23 At Astatine	24s 24 Fr Francium	24p 24 Ra Radium	25s 25 Ac Actinium	25p 25 Th Thorium	26s 26 Pa Protactinium	26p 26 U Uranium	27s 27 Np Neptunium	27p 27 Pu Plutonium	28s 28 Am Americium	28p 28 Cm Curium

[Xe] 5d ⁶ s ² 3 La Lanthanum	[Xe] 4f ⁶ s ² 4, 3 Ce Cerium	[Xe] 4f ⁶ s ² 4, 3 Pr Praseodymium	[Xe] 4f ⁶ s ² 3 Nd Neodymium	[Xe] 4f ⁶ s ² 3 Pm Promethium	[Xe] 4f ⁶ s ² 3, 2 Sm Samarium	[Xe] 4f ⁶ s ² 3, 2 Eu Europium	[Xe] 4f ⁶ s ² 3 Gd Gadolinium	[Xe] 4f ⁶ s ² 4, 3 Tb Terbium	[Xe] 4f ⁶ s ² 3 Dy Dysprosium	[Xe] 4f ⁶ s ² 3 Ho Holmium	[Xe] 4f ⁶ s ² 3 Er Erbium
[Rn] 6d ⁷ s ² 3 Ac Actinium	[Rn] 6d ⁷ s ² 4 Th Thorium	[Rn] 5f ⁶ 6d ⁷ s ² 5, 4 Pa Protactinium	[Rn] 5f ⁶ 6d ⁷ s ² 6, 5, 4, 3 U Uranium	[Rn] 5f ⁶ 6d ⁷ s ² 6, 5, 4, 3 Np Neptunium	[Rn] 5f ⁶ 6d ⁷ s ² 6, 5, 4, 3 Pu Plutonium	[Rn] 5f ⁶ 6d ⁷ s ² 6, 5, 4, 3 Am Americium	[Rn] 5f ⁶ 6d ⁷ s ² 4, 3 Cm Curium	[Rn] 5f ⁶ 6d ⁷ s ² 4, 3 Bk Berkelium	[Rn] 5f ⁶ 6d ⁷ s ² 4, 3 Cf Californium	[Rn] 5f ⁶ 6d ⁷ s ² 3 Es Einsteinium	[Rn] 5f ⁶ 6d ⁷ s ² 3 Fm Fermium

METAL ION CATALYZED CLEAVAGES OF PHOSPHONATE MONOESTERS



H_2O , pH 7.6, 30 °C, $k_{\text{hydrol}} = 2.0 \times 10^{-9} \text{ s}^{-1}$; $k_2 = 3.6 \times 10^{-11} \text{ M}^{-1}\text{s}^{-1}$

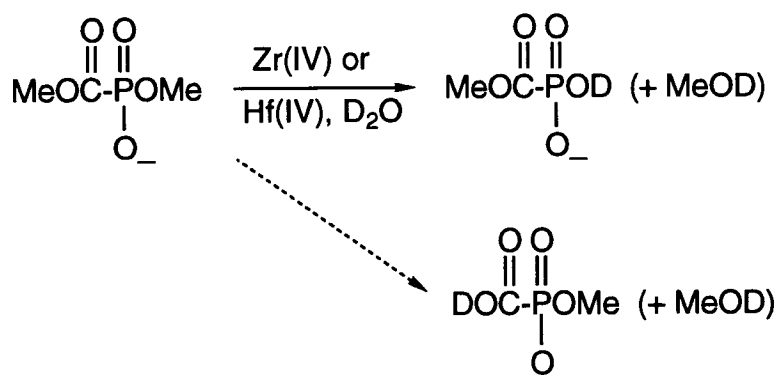
M^{4+}	pH	Brij, mM	$k_{\text{obs}}, \text{s}^{-1}$	k_{obs}/k_0
Zr^{4+}	3.5	0.0	0.11	5.5×10^7
Ce^{4+}	4.0	2.0	0.036	1.8×10^7
Th^{4+}	6.0	2.0	0.015	7.5×10^6

With 0.05 mM PNPMP, 1.0 mM M^{4+} , 37 °C.

Note enormous accelerations with Zr^{4+} , Ce^{4+} , and Th^{4+} . *Polymer or resin-bound M^{4+} might be excellent materials for the degradation of phosphonate monoesters.*

In the Zr^{4+} case, the half-life of PNPMP is reduced from 11 years to 6.3 seconds!

Zr(IV) or Hf(IV) CLEAVAGE OF DMPF

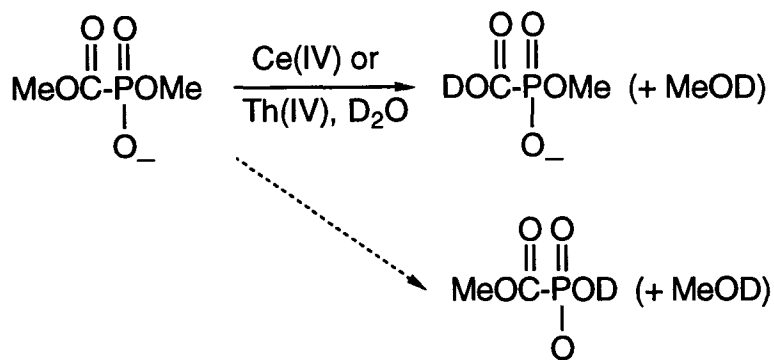


Kinetics are followed by monitoring released MeOD (^1H NMR); products are monitored by ^{31}P NMR.

M(IV)	$10^4 k_{\text{obs}} (\text{s}^{-1})$	% P-OMe	% C-OMe	$k_{\text{M(IV)}}/k_{\text{D}^+}$
Zr	4.4	79	21	3300
Hf	4.0	90	10	3100

Zr and Hf exhibit *P-O chemoselectivity*, with significant hydrolytic acceleration.

Ce(IV) or Th(IV) CLEAVAGE OF DMPF



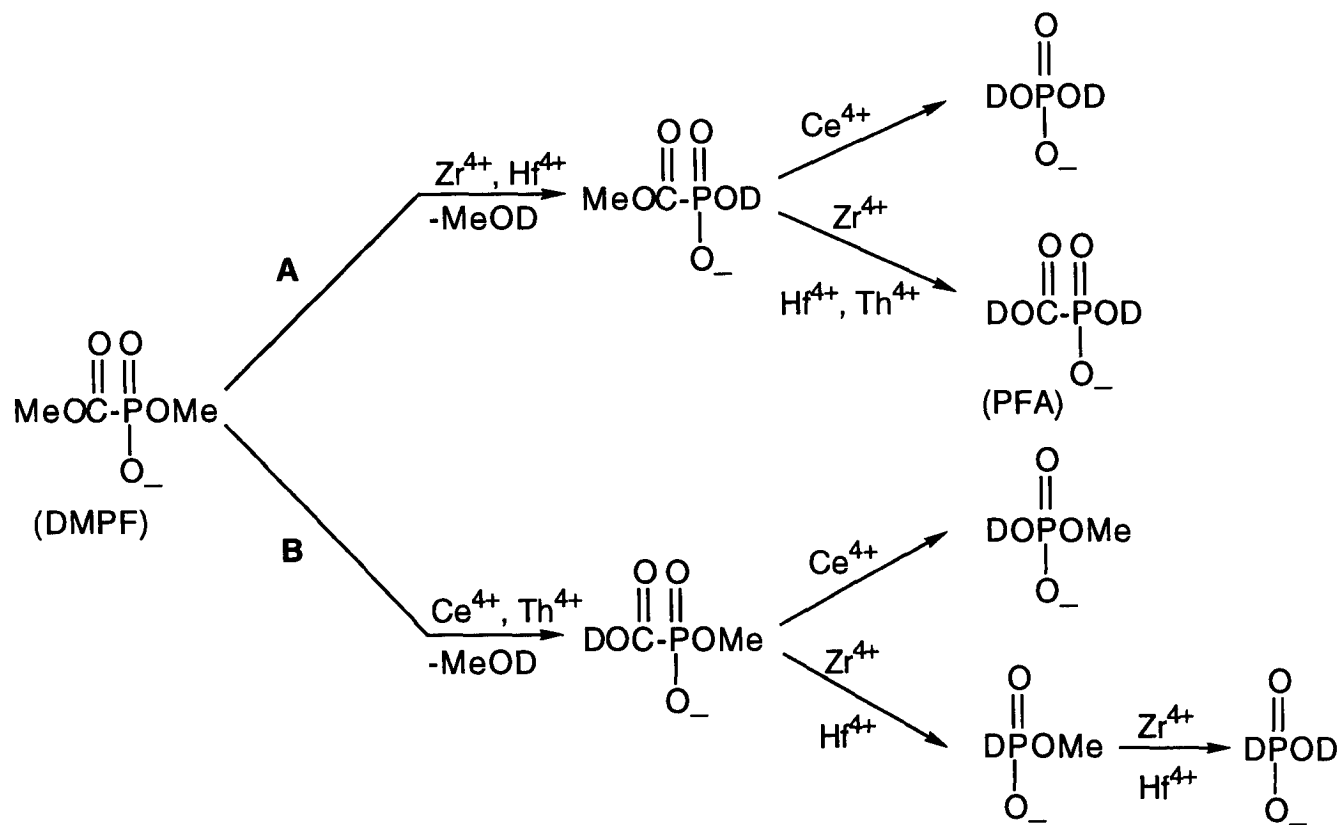
Kinetics are followed by monitoring released MeOD (^1H NMR); products are monitored by ^{31}P NMR.

M(IV)	$10^4 k_{\text{obs}} (\text{s}^{-1})$	% P-OMe	% C-OMe	$k_{\text{M(IV)}}/k_{\text{D}^+}$
Th	1.3	--	95	980
Ce	5.2	10	90	3900

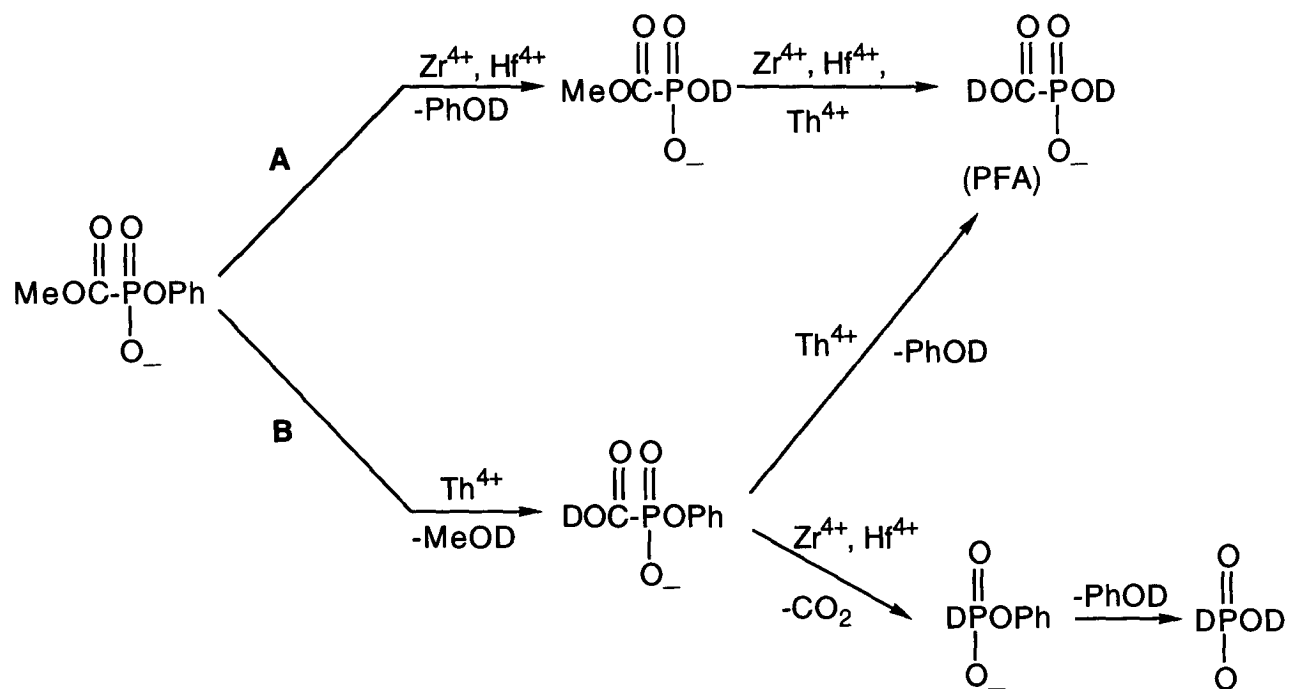
Th and Ce exhibit *C-O chemoselectivity*, with significant hydrolytic acceleration.

OVERVIEW OF DMPF REACTIONS

Cleavages of the monoesters are 10-100 times slower than cleavages of DMPF



CLEAVAGE OF C-OMe/P-OPh PHOSPHONOFORMATE



1. For Pathway A at pD 1.7 or 2.2:

$k_{\text{Zr}} = 2.3 \times 10^{-2} \text{ s}^{-1}$; $k_{\text{Hf}} = 0.65 \times 10^{-2} \text{ s}^{-1}$. Faster than DMPF cleavage.

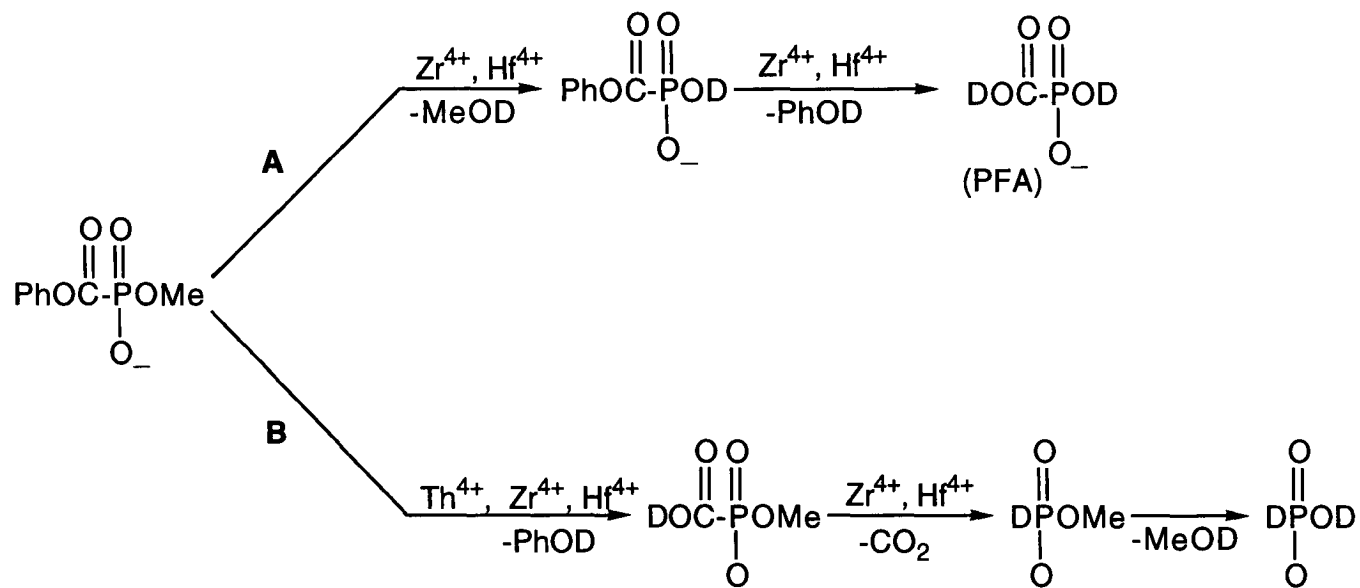
Selectivity for Zr^{4+} and Hf^{4+} is >95% P-OPh cleavage.

2. For Pathway B, Th^{4+} is >95% selective for C-OMe cleavage;

$k_{\text{Th}} = 1.6 \times 10^{-4} \text{ s}^{-1}$.

3. Chemoselectivity seen with DMPF is preserved.

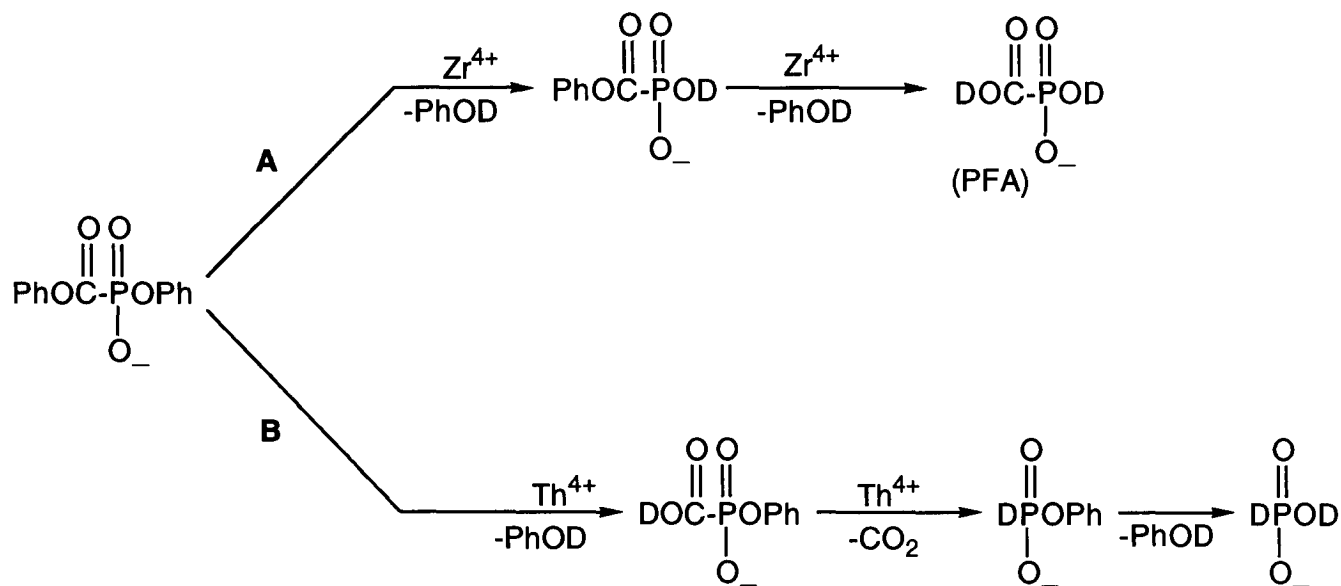
CLEAVAGE OF C-OPh/P-OMe PHOSPHONOFORMATE



With the better PhO leaving group now at C, the P-chemoselectivity of Zr^{4+} or Th^{4+} is lost. Here, C-OPh cleavage > P-OMe cleavage by 90:10 (Zr) or 79:21 (Hf): $k_{\text{Zr}} = 1.79 \times 10^{-2} \text{ s}^{-1}$, $k_{\text{Hf}} = 0.61 \times 10^{-2} \text{ s}^{-1}$.

Th^{4+} gives >95% C-OPh cleavage, as expected: $k_{\text{Th}} = 0.18 \times 10^{-2} \text{ s}^{-1}$.

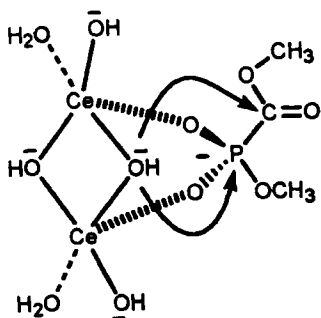
CLEAVAGE OF C-OPh/P-OPh PHOSPHONOFORMATE



1. Cleavage by Zr^{4+} was >95% P-selective; $k_{\text{Zr}} = 1.3 \times 10^{-2} \text{ s}^{-1}$ in 1:1 $\text{D}_2\text{O}/\text{CD}_3\text{CN}$ at pD 1.7.
2. Cleavage by Th^{4+} was 90:10 C-selective: $k_{\text{Th}} = 4.7 \times 10^{-3} \text{ s}^{-1}$ at pD 3.1 in $\text{D}_2\text{O}/\text{CD}_3\text{CN}$.
3. Chemoselectivity here is analogous to DMPF.

SOURCE OF CHEMOSELECTIVITY

At pH 2-3, Ce(IV) and Th(IV) will be mainly dimeric or monomeric.



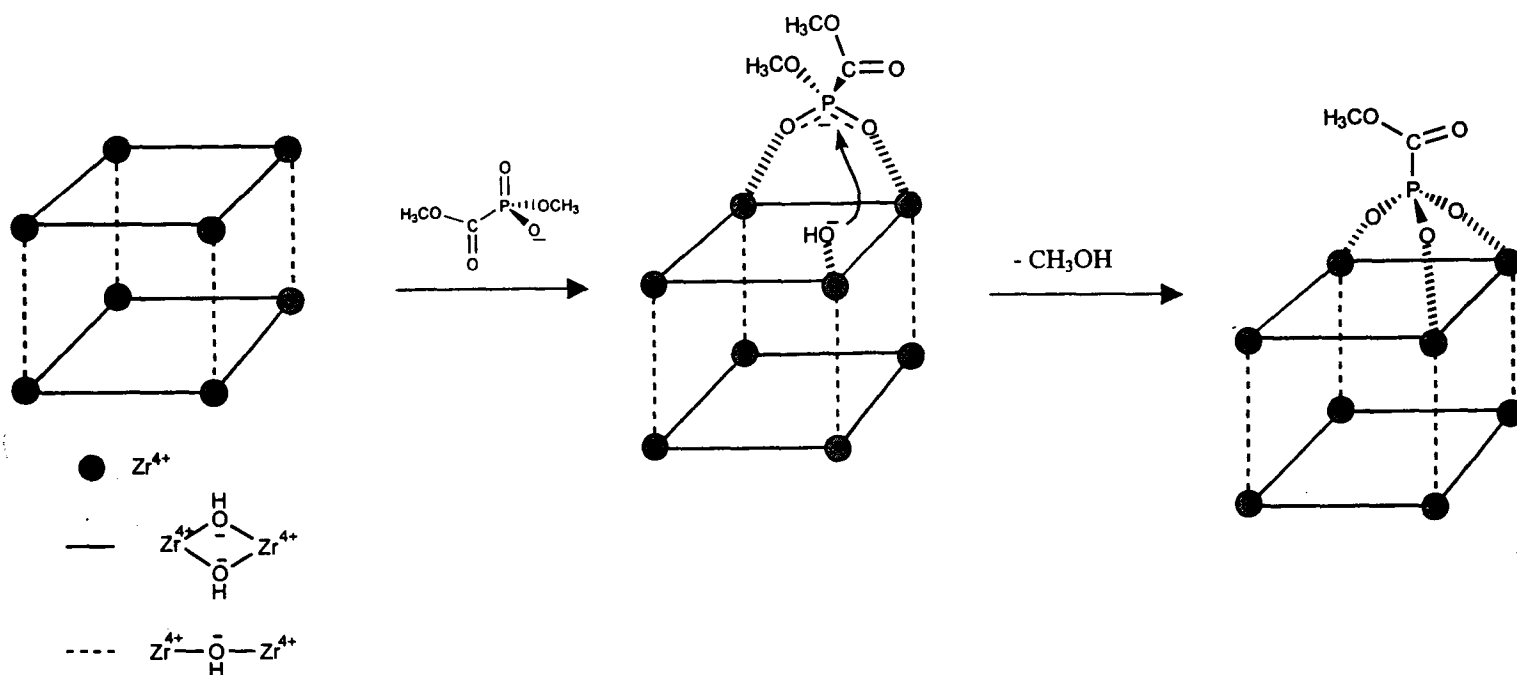
OH^- attack at $\text{C}=\text{O}$ involves a 5-membered cyclic TS; OH^- attack at $\text{P}-\text{OMe}$ involves a 4-membered cyclic TS.

Attack at *trigonal* C in 5-membered cyclic TS (addition-elimination) is kinetically preferred to attack at *tetrahedral* P ($\text{S}_{\text{N}}2$) in 4-membered cyclic TS.

Ce(IV) and Th(IV) afford C-O chemoselectivity.

P-O CHEMOSELECTIVITY

At pH ~ 2, Zr(IV), and presumably Hf(IV), exist as octamers or tetramers:



Cleavage at P can now occur via a 6-membered cyclic TS and lead directly to a tripodal phosphonate product with the same structure as the lamellar Zr phosphonates. Zr(IV) and Hf(IV) give P-O chemoselectivity.

P-O CHEMOSELECTIVITY LINKED TO M(IV) OCTAMERS

	P-O		C-O	
	Zr	Hf	Zr	Hf
M(IV)	79	90	21	10
M(IV) + Tris (1:1) ^a	40	66	60	34
M(IV) + Tris(1:2) ^a	15	19	85	81
M(IV) + NaOD (1:1) ^b	50	58	50	42

^aTris forms 1:1 complexes with Zr(IV). ^b OH⁻ promotes formation of Zr oligomers.

Destruction of M(IV) octamers/tetramers shifts P-O to C-O chemoselectivity.

SUMMARY

1. Ce^{4+} , Th^{4+} , Zr^{4+} , and Hf^{4+} ions accelerate the hydrolysis of phosphonoformate diesters.
2. With identical C-OR and P-OR leaving groups, Zr^{4+} and Hf^{4+} direct scission to the P-O ester site, whereas Ce^{4+} and Th^{4+} mediate attack at the C-O site.
3. Leaving group efficiency ($\text{PhO} > \text{MeO}$) can modulate the chemoselectivity.
4. P-O selectivity is associated with tetrameric or octameric forms of Zr^{4+} or Hf^{4+} aqueous complexes.
5. C-O selectivity is associated with dinuclear or mononuclear forms of Ce^{4+} or Th^{4+} .